Existing and Evolving Bioethical Dilemmas, Challenges, and Controversies in Vascularized Composite Allotransplantation: An International Perspective From the Brocher Bioethics Working Group

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Abstract. Early results of hand and face transplants and other grafts such as those of uterus, penis, trachea, larynx, or abdominal wall have confirmed the potential for vascularized composite allotransplantation (VCA) to restore appearance, anatomy, function, independence, and social integration in patients suffering from devastating tissue deficits untreatable by conventional treatment options. Despite such promise, these novel and complex procedures face challenges and controversies that remain open to discussion and debate. Indeed, many barriers to clinical advancement and negative stakeholder perceptions still exist. The bioethical challenges surrounding VCA include but are not limited to justice and vulnerability of subjects, and their experiences with risks, benefits and outcomes, provider economy of fame, public awareness and attitudes toward transplantation, and policy and regulatory issues shaping progress of the field. The First International Workshop on Bioethical Challenges in Reconstructive Transplantation was organized by the Brocher Foundation in Hermance, Switzerland. VCA professionals representing teams from across the world examined bioethical issues in VCA related to standards for safety, efficacy, feasibility, privacy, confidentiality, and equitability. Key discussion topics from the workshop were included in a survey questionnaire implemented across VCA professionals attending the 13th Congress of International Society of VCA held in Salzburg, Austria. The insights from the Brocher workshop and International Society of VCA survey as presented here could help inform the future development of clinical practice and policy strategies in VCA to ensure value, accessibility, and acceptance of these procedures by potential donors, potential or actual recipients and their families, and providers and payers.

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INTRODUCTION

The technical, immunological, and functional feasibility of vascularized composite allotransplantation (VCA) as a promising reconstructive/restorative option has been established for procedures such as hand or face transplantation.[1] Despite over 250 VCA procedures across the world to date, and significant federal funding for research in improving safety, efficacy, and applicability of VCA, much remains to be understood in the areas of immunosuppressive risk, rigorous adherence to medications or rehabilitation, and psychosocial issues.[2] Broader impact and clinical feasibility for VCA will be difficult to realize if bioethical concerns involving key stakeholders such as the public, patients, providers, and payers remain unresolved.[3]

The First International Workshop on Bioethical Challenges in Reconstructive Transplantation was organized at the Brocher Foundation in Hermance, Switzerland, on May 9–12, 2017. Ethical concerns about VCA had received attention in the peer literature and media over the past 2 decades. However, there was no formal discussion of contemporaneous or emerging bioethical challenges in VCA under the auspices of either the American Society for Reconstructive Transplantation or International Society of VCA (ISVCA). With over 250 transplants to date, many VCA experts agreed that the maturity of the field and long-term insights necessitated a concentrated focus on

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the bioethical implications. This was the impetus for the Brocher workshop, which was the first formal discussion of the bioethical dilemmas, challenges, and controversies that beset the field of VCA. The primary goals of the Brocher workshop were to facilitate an in-depth consideration and delineation of the bioethical issues pertinent to VCA research and practice and make recommendations to promote ethical conduct of VCA procedures.

This first formal international exploration of bioethics in VCA brought together from across the world pioneers and experts in clinical VCA, bioethicists, psychologists, and organ procurement professionals, as well as opinion leaders in the humanities, health economics, law, and policy to clarify and explore the spectrum of ethical issues raised by VCA. We present the most important themes and topics discussed at the Brocher workshop and key recommendations made by the expert panels.

Candidate Vulnerabilities

The participants at Brocher accept the notion that VCA candidates may be regarded as especially vulnerable. The special vulnerability of VCA candidates is underscored by their willingness to endure significant treatment and rehabilitation burdens and accept substantial risks for nonlife-saving VCA to participate in research protocols with unknown long-term outcomes. Given the vulnerability of candidates, those at Brocher emphasized that special protections must be in place to ensure that they are fully informed of the risks and benefits of these procedures.[4] Among the ideas put forward were improved patient decision aids, such as exposure to a range of peers including those who had decided against VCA and those who had successfully undergone the treatment, and the use of an independent patient advocate to accompany and advise the patient in interactions with the medical team. Given that those most eager to have VCA may also be the most desperate and least able to cope with the stringent demands and inevitable setbacks in treatment, improvements in psychosocial screening were also seen as a means of optimizing patient selection compatible with the best predicted graft outcomes.[5]

Patient Experiences

Patient experience was recognized as an underutilized resource for quality improvement in VCA. Further research was recommended in the challenges and burdens experienced and perceived by patients and what they might change about the process. This could be particularly valuable for addressing patients' problems with adherence to immunosuppression, physiotherapy, and follow-up care management. The collection of data on patient experiences could also assist in developing definitions of what constitutes success in VCA and improving informed consent. Some participants noted that body image matters more to some recipients, while others place a higher priority on function.[6]

Justice and Respect for Dignity

The participants discussed whether it was just to dedicate precious and limited institutional and public resources to support emerging or unproven VCA procedures despite their potential benefits to select individuals, when those same resources might meet more impactful needs of the population or preventative health.[7] There was an agreement that the ethical justification of VCA requires that the issue of justice, or fairness in the allocation of scarce resources, be taken seriously. The participants recommended that essential steps in determining need for VCA as a treatment in eligible subjects were to consider the impact of VCA on the treatable defect for the candidate's sense of dignity and thoroughly evaluate alternative options for VCA.[8,9] In light of the major burdens and risks, it was argued that while it would be unethical to pursue VCA without a thorough exploration of alternatives, it remains plausible that for some people, the alternatives may be inadequate and VCA may be the only option. The Brocher group affirmed that respect for dignity must also extend to donors and donor families with due planning for preserving donor body integrity as much as feasible following VCA procurement.[10]

Privacy Concerns

The ethical duty to protect the privacy of patients and donors is beyond dispute, but the challenges involved in doing so in VCA are great. Participants at Brocher acknowledged the challenges and inherent conflict between physician desire or institutional eagerness for publicity and the recipient or donor right to privacy. It was agreed that both recipients and donor families should be advised that the identity of recipient and donor is likely to become public, despite the most comprehensive policies and procedures to maximize privacy.[11]

Procurement, Allocation, and Policy Issues

Unlike standardized procurement and allocation systems for solid organs (heart, lung, liver, kidney, and pancreas), VCAs continue to be procured and allocated on an ad hoc basis.[12-14] Concern was expressed at Brocher for how requests for VCA donations might negatively impact willingness to donate life-saving organs. Publicity and public education about the possible donation of faces, upper extremities, penises, and uteri must be carefully managed so as not to discourage donor registration in explicit consent countries or cause individuals in presumed consent countries to opt out.[15] Additional concern was expressed about the importance of designing policy and methods of procurement which honor the dignity of donors and their next of kin. Questions were raised about whether presumed consent or first-person authorization should be regarded as sufficient or whether next-of-kin assent should also be required. The group also considered whether potential VCA donation choices (face, upper extremities, penis, uterus, etc) ought to be explicitly listed on driver license consents and authorized by potential donors.[16] It was acknowledged that transparency is vital and much work is needed in this area.

Subject Selection

Subject selection has received a great deal of attention in the literature, primarily because nonadherence to immunosuppression and physiotherapy has played a large role in poor outcomes.[6] Subject selection is an ethical concern both on the grounds of justice (fairness) and the grounds of beneficence and nonmaleficence. It would clearly be unethical to transplant a patient without due diligence in selection to assure an excellent chance of success. Discussion

on this topic at Brocher on standards for exclusion focused on the need for the identification or development of more reliable psychosocial screening instruments. It was recommended that programs must be open to the use of psychotherapy to help resolve conditions that would otherwise exclude candidates.

Risk-benefit Issues

Prominent in the discussion of risk-benefit analysis was the recognition of the substantial burdens placed on recipients and their loved ones. In many cases, wages or employment may be lost due to protracted rehabilitation or demands on recipient caregivers.[17] The Brocher experts pointed out that travel to and from the transplant center for screening and postsurgical follow-up, careful following of the medication regimen, daily self-monitoring for signs of rejection, and rigorous long-term physical therapy were some of the foreseeable burdens for patients. They felt that alongside these burdens, the risks of rejection, graft loss, opportunistic infections, the development of new metabolic diseases, and even death create the need for a very substantial and highly justifiable benefit to support a transplant whose goal is not to save the life or extend the life span of the recipient. This, in turn, raises questions about what degree of injury or functional impairment should be regarded as necessary in a recipient to be considered for VCA. It was noted at Brocher that the definitions of success and failure in different VCA were complicated or controversial and challenge consensus. They demanded an urgent discussion of these criteria among VCA teams with inclusion of physician, patient, and caregiver input.

Program Standards

Given the risks and burdens imposed on the patients and the great cost to society involved in VCA, the Brocher participants noted that the principles of nonmaleficence and justice must be implicated in the call for high program standards.[18] However, not all programs have adhered to high standards, leading to exceptionally poor results in some programs. There was uniform agreement among participants that program quality is essential for the ethical justification of VCA and international program standards must be established and enforced by every center performing VCA. The Brocher group discussed the rapid increase in the number of centers seeking program approval and the potential for a dilution of quality, as experience at any given center may be limited by scarce resources, a small pool of appropriate candidates, or other factors. Limiting the number of centers to those institutions with established expertise in VCA that was supplemented by high-volume, solid organ transplant program support could help in improving the quality of outcomes. It was noted that pressure can be high in some academic centers to justify enrollments for federally funded grants to meet milestones or merely to achieve firsts in VCA with teams or institutions rushing the process.

Informed Consent

The discussion at Brocher on informed consent focused on the following major concerns: the first was about the information owed to candidates on VCA, how it should be delivered, and how understanding should be assessed.[19] The second concern was related to the burdens, commitments, and demands of VCA that include adherence with long-term immunosuppression and follow-up recommendations and often engagement in years of physiotherapy for optimal results.[20] It was recommended that new information on outcomes (especially risks/complications) be shared with patients verbally and in writing and integrated into the consent. Such ongoing updates to the consent of patients could improve compliance with transplant recommendations and enable informed patient participation in their own care management. The Brocher group recommended the use of the informed consent as a dynamic covenant to promote a stronger sense of postsurgical accountability in patients and caregivers.[21]

Physician and Program Responsibility and Accountability for Outcomes, Public Trust, and the Perception of VCA

The novelty or relative rarity of VCA procedures and their transformational impact on patients with devastating tissue defects has contributed to their sensationalism in modern media.[22] Brocher participants uniformly concurred that sensationalistic portrayals fail to fairly represent the burdens, risks, and disappointments even in the cases with the best outcomes.[23,24] Equally important, the Brocher group strongly urged providers to refrain from the seduction of economy of fame in VCA, as it could irreparably damage public trust.[25] In this regard, meeting participants highlighted the ethical obligation for timely and transparent disclosure of successes and complications or failures by teams in the peer literature. Transparency facilitates the development of public trust, which is critical for future funding and to encourage donation. They expressed serious concern that a few programs in the field have not been faithful in publishing their results, obscuring the true picture of setbacks or advancements. Timely reporting can help identify best practices and prevent harm to other transplant recipients. The Brocher participants noted that treatment teams must honor the contributions of the recipient to the research enterprise as it is the recipients who shoulder the greatest risks and burdens, even as they hope for benefit.

Patient Responsibility and Accountability

In many ways, being a VCA recipient is akin to having a chronic progressive illness. The Brocher group noted that graft survival and function, as well as the quality of life, depended a great deal on the consistent, active participation of the recipient in his or her own care. That participation, in turn, depends, in part, on the quality of the relationships the recipient has with others, including the medical team.

Discussion focused on what it was reasonable to expect of recipients, how best to communicate effectively what is expected, and when and how to hold recipients accountable for their actions that impact transplant outcomes. It was felt that further research was needed to understand why recipients sometimes fell short of what was expected and what interventions were most effective in such situations. In light of these aspects of VCA, the Brocher group recommended close attention to the therapeutic alliance over the whole course of the treatment. The foundation for the alliance may be established in the informed consent

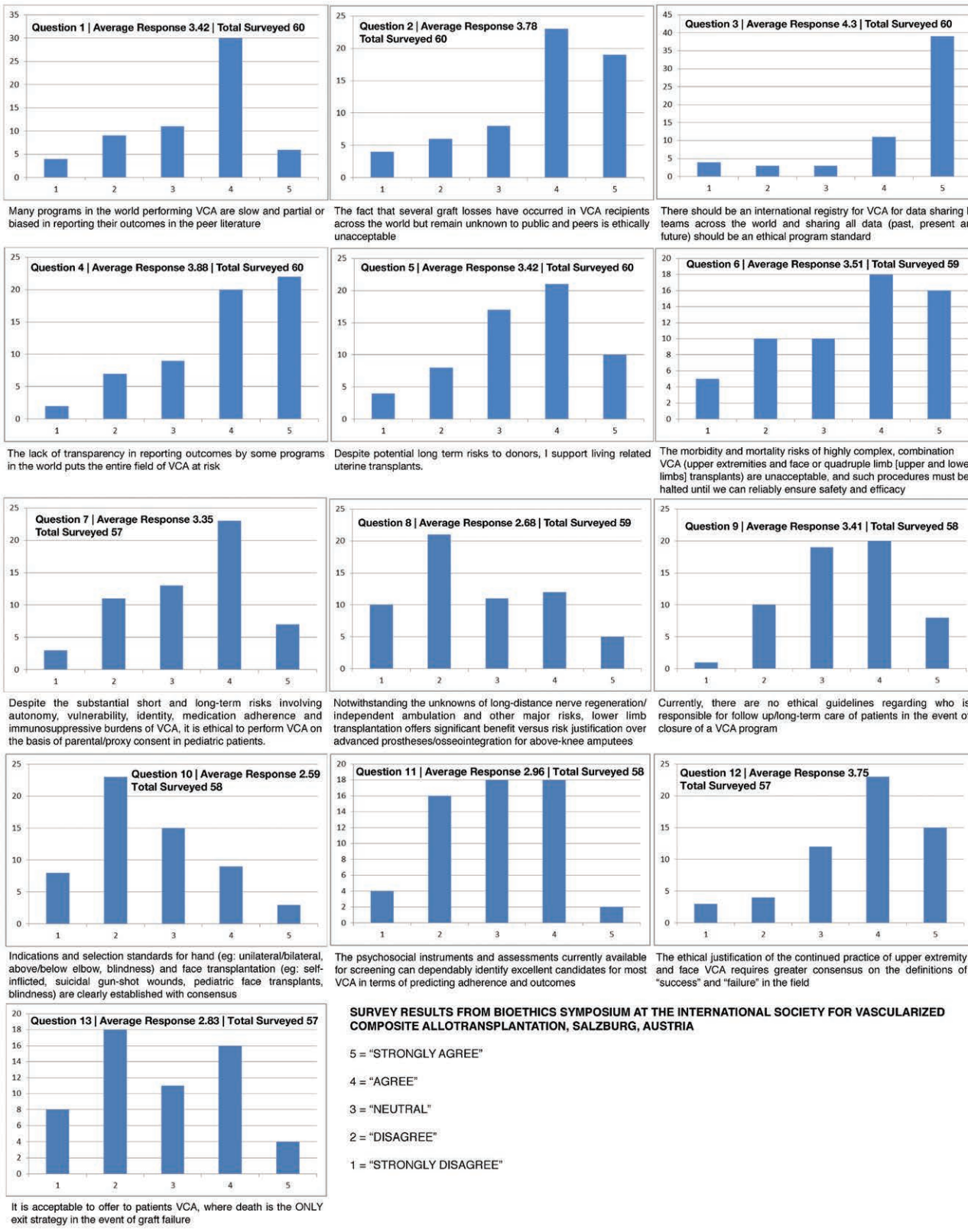

FIGURE 1. Survey results from the Bioethics Symposium, International Society of Vascularized Composite Allotransplantation 2017, Salzburg, Austria. The survey results are shown with average response and total response numbers based on a Likert-type, 1 to 5 response scale, with 1 indicating strongly disagree, 2 indicating disagree, 3 indicating neutral, 4 indicating agree, and 5 indicating strongly agree (see key). The total number of survey participants was 60. VCA, vascularized composite allotransplantation.

phase and reinforced with ongoing disclosure of new information to patients with emphasis on open communication and mutual accountability.

Exit Strategies

Finally, in light of the perpetual possibility of graft loss and high probability of eventual graft loss, it was agreed

TABLE 1.

Interpretation of bioethics survey response

Question 1	The ratio of respondents who agreed or strongly agreed that many programs are slow, partial, and biased in reporting outcomes to those respondents who disagreed or strongly disagreed was almost 3:1.
Question 2	The ratio of respondents who agreed or strongly agreed that it is ethically unacceptable to not disclose graft losses to those respondents who disagreed or disagreed strongly was >4:1.
Question 3	The ratio of those who agreed that full data sharing must be a program standard to those who disagreed was 7:1.
Question 4	The ratio of those registering agreement or strong agreement with the statement that lack of transparency puts the entire field at risk to the number registering disagreement or strong disagreement was almost 5:1.
Question 5	The ratio of those supporting living-related uterine transplants to those opposing it was >2:1. However, almost one-third of respondents were neutral.
Question 6	While respondents leaned toward halting combination VCA, only slightly more than half (54%) either agreed or strongly concurred with this recommendation.
Question 7	The ratio of those who agreed that it is ethical to perform pediatric VCA on the basis of proxy (parental) consent to those who disagreed was >2:1. However, nearly one-fourth of respondents were neutral on this issue.
Question 8	The ratio of respondents who felt that lower limb transplantation did not offer benefit vs risk over prostheses for above-the-knee amputation compared with those who believe it did was almost 2:1.
Question 9	Respondents leaned toward agreement that there are no ethical guidelines regarding responsibility for follow-up, but almost a third of respondents were neutral.
Question 10	The ratio of respondents who did not seem to feel indications and selection standards for hand and face were clearly established with consensus, to those who considered them as well established was with a >2:1 ratio. However, more than one-fourth of respondents took a neutral stance.
Question 11	Middle positions (agree/neutral/disagree) predominated and were balanced around the question of the ability of current psychosocial screening to identify excellent candidates. We are clearly far from consensus on this matter.
Question 12	The respondents leaned heavily (38:7) in the direction of agreement or strong agreement in response to the statement that the ethical justification of VCA requires greater consensus on definitions of success or failure in the field.
Question 13	On the question of whether it is ethical to offer VCA in which death is the only exit strategy, middle positions (agree/neutral/disagree) predominated and were roughly balanced. Stronger opinions (strongly agree or strongly disagree) were less frequent than in many other survey questions.

Questions 1 to 4 addressed the importance of transparency and reporting. The results show strong support for improvements in this area. Questions 5 to 8 and 13 addressed benefit-risk. Respondents were quite divided on these issues. Questions 9 to 12 dealt with program standards. The diversity of opinion in the field was reflected in the responses to these questions, with the only solid directional preference coming in response to the suggestion that there was a need for greater consensus on success and failure definitions.
VCA, vascularized composite allotransplantation.

that there is an ethical duty to thoroughly consider all known exit or life-boat strategies before transplantation. The Brocher group agreed that exit strategies are complex and could be unique to particular VCA, with face transplants having the greatest risk profile. In the event that a second transplant is not feasible and if there is not a sufficient amount of tissue available for autologous reconstruction, the loss of a face graft could be fatal.[26] It is, therefore, ethically imperative to attempt to determine the likely alternative options to VCA and end outcomes of VCA and discuss these as part of the consent process.

Following the Brocher workshop, the most important bioethical questions that were discussed at the meeting were formulated into a survey questionnaire, which was implemented across VCA professionals attending the 13th Congress of ISVCA held in Salzburg, Austria in October 2017.[27]

The results of the ISVCA meeting survey are summarized in Figure 1. These 13 questions spanned the some important bioethical dilemmas and challenges surrounding these procedures. The surveyed pool of 60 participants represented key stakeholders in VCA who were in attendance at the ISVCA meeting. These included an international group of VCA surgeons, transplant physicians, immunologists, physical therapists, psychologists, bioethicists, transplant social workers, and organ procurement professionals. The interpretation of the anonymous survey shed valuable and interesting insights into the perceptions and attitudes as well as biases among the participants in their responses to key bioethical questions in VCA (Table 1).

Taken together, the purpose of the Brocher workshop and ISVCA survey was not to seek consensus but obtain critical early insights into the state of bioethics in VCA to help direct meaningful debate and recommendations for improvement. The common themes that emerged from both the workshop and survey are the following:

There is a need for prompt, rational, effective, objective, rigorous, and deliberate evaluation of the bioethical impact and implications of existing and novel therapeutic options for individual VCA procedures by all programs.

Providers must bear the ethical responsibility to maximize benefits and optimize outcomes of VCA and facilitate validation of safety, efficacy, and feasibility of protocols across participants from different demographic, ethnic, and etiopathologic groups.

VCA programs must ensure open data sharing and transparent, timely disclosure of outcomes to peers and public.

Programs must collaborate more and agree on study standards, uniform assessments, or data points and pooling of data or comparison of results among centers (that individually lack necessary sample size or randomization). This could increase generalizability of outcomes after VCA and may indeed be the best means of increasing the quality of

evidence for clinical decision making, provide objective cost analysis,[28] and inform health policy for approval and adoption of a given VCA as a standard of care, safe, effective, and ethical therapeutic option.[29,30]

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